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Review on Pharmacoscintigraphy

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Authors' contributions

This review was carried out in collaboration among all authors. Author PVKK gathered details of manuscript and contributed in writing the manuscript regarding this review topic. Author SA contributed in collecting the information from various books. Author YSR analyzed these data and necessary inputs were given towards the designing of the manuscript. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Pharmacoscintigraphy is a non-invasive technique for determining the fate of drugs after administration into humans. Collecting valuable information through the pharmacoscintigraphy about absorption and release mechanisms of drugs from formulations, and thus proving to be an invaluable tool in developing newer and more effective formulations. Such studies can be used to determine the behavior of drugs, formulation as well as diagnostic agents that are administered. In this technique, radiolabelled formulations are administered to patients by their intended route of administration. Their transit through the body is monitored using sophisticated imaging cameras. Since the amount of radiotracer that is used is very low, this is a safe, efficient, and accurate method for studying the behavior of drugs in the human body. Preclinical studies of newer drugs have successfully been carried out using the pharmacoscintigraphic technique.

Keywords: Gamma-emitting isotopes; neutron activation; gamma camera; colon targeted.

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1. INTRODUCTION

Investigation of pharmacokinetic parameters of a new drug moiety involves analysis of the drug/metabolite levels in plasma and urine over a long period. Various methods for determining the fate of the drug in the body are well established and reported in the literature [1]. However, these methods are invasive, lengthy, cumbersome, expensive, and inaccurate. Also, they failed to provide vital information about the biopharmaceutics of the drug i.e. interrelationship of physical/chemical properties of the drug, dosage form, route of administration, or rate and extent of systemic drug absorption. This drawback has been addressed to a certain extent by carrying out *in-vitro* tests on the formulations and correlating them to *in-vivo* parameters (*in-vitro in-vivo correlation*) and using the same to predict the effect of formulation changes on the in vivo performance of the drug. However, IVIVC has several short comings [2].

The technique of gamma scintigraphy, which involves the use of gamma-ray emitting radioisotopes, has been used to study the path of the drug in the human body after the administration. In this technique, a gamma-emitting radionuclide is tagged with the drug/formulation under investigation [1]. It is then administered via the intended route of administration and the volunteer is scanned under the camera to obtain vital information. The major advantages of this technique include high throughput screening at the preclinical stage, objective zero phase human trials, reduced sizes of other phases of clinical trials, a significant reduction in development cost and time [3].

Evaluation by pharmacoscintigraphy involves the administration of radiolabeled dosage form. Drug/formulations can be radiolabelled either by gamma-emitting isotopes or by neutron activation technique [4]. Further, emitted radiations are captured by external detectors, such as gamma cameras.

2. PHARMACOSCINTIGRAPHY

Gamma scintigraphy is a well-established technique for the diagnosis of various diseases in neurology, oncology, and cardiology. Pharmacoscintigraphy is the application of gamma scintigraphy technique. This technique is based on tracing the path of the radiolabelled ingredient of the formulation from the delivery system to the gastrointestinal tract, then into the systemic circulation. The radiolabelling of active ingredients or any excipients of the formulation can visualize the delivery system under the gamma camera. It can be used in the evaluation of:

1. New drug molecules
2. New drug delivery systems/formulations
3. Therapeutic drug monitoring

New drug molecules need to be evaluated for their pharmacological responses at the preclinical stage. Quantitative assessment of a molecule in organs is a cumbersome job. Moreover, bio-distribution studies are feasible in only small animals at this stage. Pharmacoscintigraphy however takes an upper hand by making use of the radionuclide as a marker for the drug molecule in each organ and assessing the concentration of the drug by counting the radioactivity in the organs [2]. By injecting the radiolabelled molecule intravenously into the subject the dynamic picture of the drug deposition and clearance from the organs can be studied and then imaging under the gamma camera. The organ or the organ system can be highlighted to study the pharmacological response.

2.1 Advantages

1. Novel drug formulations and delivery systems are easily evaluated.
2. Method to determine drug distribution profile.
3. Precisely depicts the drug release and absorption pattern.
4. The current location and behavior can be easily visualized and analyzed.
5. The science of scintigraphy simplifies the estimation of the absorption and distribution profile of radiolabelled drug formulation/delivery systems administered through a suitable route.
6. Comprehensive technique for the evaluation of all the targeted drug delivery systems used for brain targeting, Kidney targeting etc.
7. Determines the complex organ structures and so the accurate drug dose can be judged to be made bioavailable in case of inhaler and pulmonary drug delivery systems.

2.2 Disadvantages

1. Very little anatomical information is gained, unless the formulation outlines easily

recognizable organs, such as the stomach and large bowel.
2. When non-disintegrating matrix systems are studied, identification of the position of the object becomes difficult, and it is necessary to administer a second radiopharmaceutical to outline the GI tract.
3. The technique is unable to accurately quantify the activity in the small bowel because of its coiled nature.
4. Gamma scintigraphic assembly is expensive, and the method requires qualified personnel for operation.
5. It is not possible to label all compounds/drugs of interest. This disadvantage can be overcome by labeling one of the excipients.

3. RADIOLABELLING OF FORMULATIONS

3.1 Labeling by Gamma-Emitting Isotopes [5,6]

Radiolabelling includes usage of a short-lived radioisotope that can suddenly transmit gamma radiation. Regularly 131Iodinated proteins, technetium (99Tc) labeled compounds are utilized in gamma scintigraphy. The isotope is incorporated in the formulation as a salt (e.g. sodium per-technetate). In this type of labeling, a reducing agent is used to reduce technetium, Tc (VII), into a lower valence state [5]. The final solution is maintained in a buffered system, which is followed by incubation with drugs to enable labeling. The most widely used reducing agent is the acidic stannous chloride or other stannous salts. Different methods for radiolabelling can be classified into whole dose radiolabelling, point radiolabelling, and surrogate marker technique. Normally utilized radionuclides are in Table 1 alongside their half-life.

3.2 Labeling by Neutron Activation Technique [7-10]

This method involves the incorporation of a stable isotope before its manufacture, followed by neutron irradiation of the intact dosage form (Table 2). Neutron flux exposure is conducted generally for 5-30 seconds over a very short time. This exposure time also prevents the degradation of drug under conditions of bombardment [7]. Longer exposures may result in cross-linking of the polymers used in the dosage form. Short exposure time also prevents the degradation of the drug under conditions of bombardment. During this technique, thermal neutron irradiation converts the carefully selected stable isotopes Samarium or Erbium (152Sm or 170Er) into radioactive gamma-emitting isotopes (153Sm or 171Er) that can be detected by external imaging devices [8]. The radioactive dosage form is then administered through the intended route of administration. The way that it follows is determined by a gamma camera. Generally a gamma-emitting radionuclide (99mTc) is used in this procedure [9].

Table 1. Commonly employed radionuclides

Radionuclide	Half-life (approx.)
^{81m}Kr (Krypton)	13 sec
^{99m}Tc (Technetium)	6.02 h
^{111}In (Indium)	2.8 d
^{123}I (Iodine)	13 h
^{131}I (Iodine)	8.0 d

3.3 Gamma Camera [11]

Gamma camera helps in the detection of radiations emitted from a radionuclide. Gamma camera is used to image the gamma radiation which is emitted from radioisotopes. Nuclear imaging is predominantly carried out with planar or SPECT (single-photon emission computed tomography) cameras and by using radionuclides that emit gamma radiation with energies between 100 and 250 KeV. Single-photon emitting radioisotopes such as 99mTc (Technetium) and111In (Indium) are widely used with these instruments. Gamma camera is composed of an array of photomultiplier tubes coupled to a sodium iodide crystal [11]. The interaction of emitted gamma photons from the source with the crystal leads to the production of a flash and it is detected by a photomultiplier. A good depiction of the position of the radiotracer is provided by the planar image. For this reason, radiolabelled drug delivery systems are best studied with a planar camera [12]. SPECT should be considered if planar imaging cannot provide the required deposition details. SPECT is a technique used for producing cross-sectional images of radionuclide distribution in the body. This is achieved by imaging the organ at different angles (eg. 64 or 128 images / 1800 or 3600) using a rotating gamma- camera. The acquired raw data are then processed by high-speed computers.

4. APPLICATIONS OF PHARMACOSCINTIGRAPHY

It has found wide applications in conventional as well as novel drug delivery systems for evaluation at developmental, preclinical as well as clinical stages [10]. So with the combination of pharmacokinetic studies with scintigraphy has also become an important means of providing information about the transit time and the release behavior of dosage forms along with subsequent drug absorption patterns.

4.1 Oral Drug Delivery System

The oral route is one of the most convenient routes of drug administration. It has the least patient non-compliance. Both conventional as well as sustained release can be determined in the oral dosage forms with the help of pharmacoscintigraphy. The behavior of capsules coated with polymers HPMC K100M and HPMC K4M was studied using the pharmacoscintigraphy technique by Honkanen et al. [13]. Metoclopramide hydrochloride and ibuprofen were used as model drugs. Scintigraphic studies revealed that HPMC K100M disintegrated in 8 hours while HPMC K4M was almost intact. Also, the spreadability of HPMC K100M was superior when compared to that of HPMC K4M. HPMC K4M also showed the tendency of plug formation. This technique also finds application in the study of gastrointestinal mobility. Guaiphenesin was labeled with Samarium (153Sm) and loaded on to ion exchange resins by Yeong et al. [14]. The drug-loaded resins were filled into capsules and administered to healthy volunteers, to study gastrointestinal mobility as shown in Table 3.

Table 2. Properties of radionuclides utilized in neutron activation based scintigraphy

Stable nuclide	Natural abundance (%)	Radionuclide	Half life	Daughter nuclide
^{138}Ba (barium)	71.7	^{139}Ba	83min	^{139}La (stable)
^{170}Er (Europium)	14.9	^{171}Er	7.5hr	^{171}Tm ($t_{1/2}$ = 1.9y) ^{171}Yb (stable)
^{153}Sm (Samarium)	26.7	^{153}Sm	47hr	^{153}Eu (stable)

Table 3. Evaluation of oral drug delivery systems by pharmacoscintigraphy

Drug	Formulation	Research envisaged	Pharmacokinetic data	Reference
Naproxen	Tablet	Tablet disintegration and onset of absorption	Close correlation between tablet coat disruption and detection of drug in plasma	Hardy et al. [15]
Theophylline	Tablet	*in vitro–in vivo* correlation	Correlation of absorption data with *in vitro* release kinetics	Sournac et al. [16]
Aminophylline	Tablet	*In vitro–in vivo* correlation and relationship of dosage form position to serum concentration	Absorption of drug independent of tablet position and controlled by release from the tablet.	Davis et al. [17]
Naproxen	Multiple unit dosage form	Disruption of pellet coating and onset of absorption	Close correlation between tablet coat disruption and detection of drug in plasma	Hardy et al. [18]

4.2 Gastro Retentive Drug Delivery System

Improvement of rate – controlled oral medication conveyance frameworks for beating physiological misfortunes, for example, gastric residence times, unpredictable gastric emptying times, and so forth., has prompted developments, for example, gastro retentive medication conveyance systems [19]. Also variable absorption of many drugs in the lower GIT necessitates controlled release dosage forms to be maintained in the upper GIT tract, particularly in the stomach and upper small intestine [20,21]. These approaches have gained considerable interest because they are economical and easy to deliver by conventional routes and include specialized tablets, capsules, powders, microspheres, granules, etc [22]. Besides gastric retention of the drug delivery system also enhances the bioavailability and therapeutic efficacy of drugs with a narrow absorption window in the upper part of GIT. Pharmacoscintigraphy is an effective tool for determining the fate of drugs meant to be released in upper regions of the GIT (Table 4).

Kenyon et al. investigated the fate of saquinavir gastro retentive tablets after oral administration in volunteers using the pharmacoscintigraphy [23]. The results showed that the bioavailability of saquinavir is significantly improved in the presence of food. In fasting conditions, the medication plasma fixation was limitless, yet in took care of condition the focuses were quantifiable as long as 12 hours.

4.3 Colon Targeted Drug Delivery System

Using scintigraphic imaging, information about the time of transit through the stomach and small intestine, and time of arrival of a colon-specific colon-specific drug delivery system in the colon can be obtained. Information about the spreading or dispersion of a formulation can be elicited [26]. Such studies can also provide information about regional permeability in the colon [27]. Steed *et al.,* demonstrated the application of pharmacoscintigraphy in a study carried out for the treatment of inflammatory bowel disease [28]. Volunteers were administered three formulations enteric-coated tablets of 5-Amino salicylic acid (5- ASA). Assessment of transit/disintegration and drug absorption was carried out by pharmacoscintigraphy. A clear differentiation between the 3 formulations in terms of *in vivo* lag time, anatomical location of disintegration, and subsequent 5- ASA absorption pattern was seen. Wilding et al absorbed GI transit of formulations of diltiazem whose release was modified by using hydrophobic and hydrophilic swellable polymers [29]. Pharmacoscintigraphic investigation revealed that the drug was readily absorbed from the colon.

The evaluation of the intelisite® capsule was done by Clear et al. [30]. The device is used to deliver theophylline and furosemide tablets to the small intestine and colon. Intelisite® capsules were activated by external radiofrequency. The formulation was compared with conventional dosing to observe the absorption profile in the small intestine and colon. The gastrointestinal transit and activation of the intelisite® capsule was monitored using gamma scintigraphy. The study revealed that intelisite® capsule was successfully activated at the desired site and well-tolerated in human volunteers [31].

4.4 Pulmonary Drug Delivery System

Scintigraphic imaging places an important role in the analysis and evaluation of drug delivery via the pulmonary route. This route is preferred to all the others, when it becomes necessary to treat reversible obstructions of the respiratory tract. Using this technique, quantitative measurement of the amount of drug delivered from an inhaler device becomes easy and local bioavailability can be determined. Also, bioequivalence study can be done in a more prominent and better way. This technique is more relevant than classical bioequivalence testing for assessing the bioequivalence oh inhaled asthma medication, more appropriate than in-vitro findings, and reliable as compared to clinical response studies [32,33].

Pharmacoscintigraphic technique offers the following advantages in the evaluation of pulmonary drug delivery system [34,35].

- It reveals proof of concept in man for newer devices.
- It establishes the likely dose range of a newer inhaler device as compared to an established product.
- It helps to visualize the complex structure of the lungs in 3 dimensions.
- It provides reliable and precise information on the amount and location of drug deposited in the lung after inhalation.

Table 4. Applications in gastro-retentive drug delivery approach

Objective	Conclusion	Reference
Evaluation of the gastric retention time of the sustained release floating mini-tablets (FMT) and the marketed Prolopa® HBS 125 floating capsule in fed state.	Sustained release FMT was able tofloat on the surface of gastric fluid for more than 4 h.	Goole et al. [24]
Evaluation of the single-dose pharmacokinetics, GI transit and on release properties of a GABA receptor agonist from an endogastric therapeutic system (EGTS),using pharmacoscintigraphy in fasted and fed states in healthy volunteers.	Findings suggested that the EGTStechnology is an effectivegastro-retentive system for the delivery of therapeutic compounds.	Cumming et al. [25]

- It helps to establish the likely dose range of a newer inhaler device as compared to an established product.
- It presents accurate information with regards to inhaler design modification and process.

4.5 Engineering Aspects

Kumar et al. [36] successfully applied the pharmacoscintigraphic technique to assess the deposition of heavy metals in the lungs. The formulation understudy was nano-edetate calcium disodium (Ca – Na_2 EDTA) dry powder inhaler. Radiolabeling of drugs was achieved using 99mTc. It was evident from the study, that Ca – Na_2 EDTA exhibited higher respirable fraction and showed a significant increase in drug delivery to the alveolar region as compared to micronized form.

Ali et al. [37] successfully applied the pharmacoscintigraphic technique to study the effectiveness of fluticasone propionate nanoparticles in preventing acute lung injuries on exposure to toxic gases. When evaluated by the Anderson cascade technique, the nanoparticles were found to be far superior to the micronized form. Ventilation of lung scintigraphy of the nanoparticles in human volunteers showed a significant increase in drug delivery to the alveolar region. Thus the objective of developing a potential antidote against inhaled toxic gases was achieved and successfully demonstrated by the scintigraphic technique.

Cass et al. [38] used the pharmacoscintigraphic technique to elucidate sites of zanamivir deposition in the respiratory tract, after oral inhalation from the Diskhaler device.

4.6 Ocular Drug Delivery System

Ophthalmic preparations, including solutions, suspensions, and ointments, can be applied topically to the cornea or instilled in the cul-de-sac or conjunctival sac of the lower lid [39]. This research reported by Gupta et al. [40], was initiated to improve pre-corneal residence time and ocular penetration of Sparfloxacin. A novel colloidal system known as PLGA [poly (di-lactide-co-glycolide)] nanoparticles were developed.

Sparfloxacin, labeled with 99mTc, was incorporated in the nanosuspension. The developed formulation showed an extended-release profile. Scintigraphic images showed good retention of the nanosuspension over the entire precorneal area as compared to marketed formulation. The marketed drug formulation reached the systemic circulation through the nasolacrimal drainage system rapidly, whereas the developed nanosuspension cleared at a very slow rate and remained at the corneal surface for a longer duration.

The research work carried out by Akhtar et al. [41] reported improved ocular retention and aqueous humoral drug availability of ganciclovir (GCV). GCV was administered topically using nanoparticle carriers such as PLGA nanoparticles and chitosan-coated nanoparticles. Scintigraphic images proved the enhanced ocular corneal retention property and the slow clearance of chitosan-containing formulations as shown in Table 5.

Gamma scintigraphy has also been used by Senthil Kumara et al. [42] to confirm the involvement of efflux transporter, P-glycoprotein, in intraocular disposition of various drugs.

Table 5. Evaluation of ocular drug delivery systems by pharmacoscintigraphy

Drug / formulation	Objective	Reference
Timolol-maleate loaded chitosan/HPMC based polymer	To enhance ocular retention	Gupta et al. [40]
HEC and gellan gum formulations	To determine species-specific differences in the pre- corneal residence of two gelling agents in humans and rabbits	Greaves et al. [43]
Polyvinyl alcohol films	To study the pre –corneal residence of polyvinyl alcohol films	Fitzgerald et al. [44]
Pilocarpine nitrate containing New Ophthalmic Delivery System (NODS)	To study the rate of clearance of a soluble marker from a NODS	Greaves et al. [45]

4.7 Targeted Drug Delivery System

Nanoparticles, liposomes, microspheres, and other novel drug delivery systems are being explored as carriers of drugs to specific sites and organs in the body. Tracing the path of these targeted drug delivery systems *in-vivo* can be accomplished by pharmacoscintigraphy. This technique enables us to test these formulations in the body in a quantitative manner in a relatively short period.

5. MISCELLANEOUS APPLICATIONS

Pharmacoscintigraphy has also been proven to be a useful tool in the evaluation of new drugs during development phase [35], characterization of new formulations/ delivery systems [36,37], establishing bioequivalence of generic products, therapeutic drug monitoring [38,39], dosage forms intended for rectal route and in various site/organ targeting studies [40].

Recently, pharmacoscintigraphy has been used for evaluation of the fate of natural products in the body. Mittal et al. radiolabeled honey with 99mTc and studied its tissue distribution in the rabbit model of *Staphylococcus aureus* infection. The activity of bioactive antibacterial compounds in radiolabelled preparation was confirmed by its localization at the site of bacterial lesion. This indicates that pharmacoscintigraphy may show promise as a tool for high throughput screening of bioactive components of natural products.

6. CONCLUSION

Pharmacoscintigraphy helps in determining the actual *in-vivo* distribution pattern of the drug from the administered dosage form and is an elegant, non-invasive approach for assessment of pharmacokinetic information. This approach is also useful in the evaluation of novel carrier-based drug delivery systems administered by different routes. It also assists in organ mapping. It has proved to be an important tool in studying inter-subject variability especially the effect of food on pharmacokinetic parameters as well as for establishing windows of absorption for oral drug delivery. The amount of radioactive tracer incorporated in the formulation is well below the maximum permissible dose, thus rendering the technique safe. It is anticipated that the advancements and newer applications of this imaging technique will play a vital role in tracking of sophisticated new generation drug delivery systems. In combination with traditional in-vivo and *in-vitro* studies, pharmacoscintigraphy is a powerful tool for studying the bio-distribution pattern of drug.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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